

(c) the  $\beta$ -galactosidase ( $\beta$ -Gal) gene; and

(d) the green fluorescent protein (GFP) gene.

*B7D  
CPK*

39. (New) The method according to claim 37, wherein the host cell endogenously expresses at least one GABA<sub>A</sub> receptor 1.

40. (New) The method according to claim 37, wherein the host cell hosts an expression system comprising a nucleic acid molecule encoding at least one transcription factor.

41. (New) The method according to claim 40, wherein the transcription factor is selected from the group consisting of: CREB-1, CREB-2, CREM-1, ATF-1, ATF-2, ATF-3, ATF-4, Sp1, Sp2, Sp3, Sp4, AP-1 and AP-2.

*Add C3*

REMARKS

I. Restriction Requirement

The restriction requirement pursuant to 35 U.S.C. §§121 and 372 was maintained despite Applicants attempted traverse of the requirement in the Preliminary Amendment and Response filed

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December 28, 2001. (See Office Action ¶1.) The invention of Group III was elected, for examination purposes, with traverse, in the Preliminary Amendment and Response.

It has been alleged that the subject application contains the following inventions or groups of inventions which are independent and patentably distinct from each other:

Group I (claims 1-20), directed to nucleic acid molecules constituting human GABA<sub>A</sub> receptor 1 promoters;

Group II (claim 21), directed to a method for assaying GABA<sub>A</sub> receptor 1 promoter activity;

Group III (claims 22-27), directed to methods of screening compounds which are modulators of GABA<sub>A</sub> receptor 1 transcription,

Group IV (claims 28 and 29), directed to transgenic non-human animals with genomes comprising human GABA<sub>A</sub> receptor 1 promoters; and

Group V (claims 30 and 31), directed to methods of screening compounds as modulators of GABA<sub>A</sub> receptor 1 activity, which methods use the transgenic animals of claim 28 or 29.

### II. Traversal of the Restriction Requirement

Applicants respectfully maintain that the restriction requirement is improper. The subject application is the national stage application of PCT/SE00/00878. Therefore, as set forth in M.P.E.P. §1850, PCT Rules 13.1 and 13.2 are to be

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followed when considering unity of invention without regard to the practice in national applications filed under 35 U.S.C. §111.

PCT Rule 13.1 provides that unity of invention exists when a group of inventions are so linked to form a general inventive concept. According to 37 C.F.R. §1.475(a) and PCT Rule 13.2, the criterion regarding unity of invention among a group of inventions is fulfilled by the existence of "a technical relationship among those inventions involving one or more of the same or corresponding special technical features." The expression special technical feature means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

In the subject national stage application, the special technical feature which defines the contribution of each of the claimed inventions over the prior art is the GABA<sub>A</sub> receptor 1 promoter, P1a or P1b. The GABA<sub>A</sub> receptor 1 promoter is a recited feature, either directly or indirectly, of each and every claim in Groups I-V.

With regard to the application of PCT Rule 13.2, the following guidance is provided by M.P.E.P. §1850:

In applying PCT Rule 13.2 to ... national stage applications under 35 U.S.C. 371, examiners

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should consider for unity of invention all the claims to different categories of invention in the application and permit retention in the same application for searching and/or preliminary examination, claims to the categories which meet the requirements of PCT Rule 13.2. (Emphasis added.)

Neither Rule 13.2 nor M.P.E.P. §1850 limits unity of invention to only those claims directed to one category, i.e., embodiment or use, of the GABA<sub>A</sub> receptor 1 of the invention. Conversely, M.P.E.P. §1850 expressly provides that the retention of all the claims in the same application should be permitted provided that the requirements of Rule 13.2 are satisfied.

It appears that the Examiner has failed to properly apply PCT Rules 13.1 and 13.2 in evaluating Unity of Invention, for the following reasons. The Examiner has acknowledged that the special technical feature of Group I is "GABA<sub>A</sub> receptor 1 promoters P1a or P1b or functionally equivalent modified forms thereof or active fragments thereof." (See Office Action, ¶1.C., lines 9-11.) This acknowledgement, if anything, supports Applicants' basis for traversal, i.e., that this special technical feature is common to all of the alleged Groups of inventions.

The Examiner has also asserted an alleged anticipation of claims 1-4 of Group I by the article of Mu et al. ("Mu"; The mouse GABA(A) receptor alpha3 subunit gene and promoter, Brain

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Res. Mol Brain Res. 67: 137-147, 1999) as a basis for maintaining the present restriction. (See Office Action, ¶1.C., lines 11-16; a copy of the Abstract of Mu is enclosed.) It is not clear how the Examiner's asserted anticipation rationale properly pertains to the question of Unity of Invention but, in any case, the rationale cannot be valid since Mu relates to GABA<sub>A</sub> and not GABA<sub>B</sub> receptor promoters. (See the enclosed Abstract of Mu.) Hence, there is no anticipation.

Thus, by reason of their direct or indirect recitation of a GABA<sub>B</sub> receptor 1 promoter, the claims are so linked as to form a single general inventive concept. As such, the requirements of 37 C.F.R. §1.475 and PCT Rules 13.1 and 13.2 are satisfied. Withdrawal of the restriction requirement is respectfully requested.

### III. Claim amendments

Upon entry of this Amendment, claims 1-41 are pending in the application.

Independent claim 22 has been amended to more clearly and particularly recite what Applicants regard as their invention. Specifically, step (a) of amended claim 22 has been restated as providing a host cell which hosts the expression system recited

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in the claim, rather than transfecting a host cell with the expression system. Dependent claim 26 has been amended to embody terminology consistent with amended claim 22. Further, claim 22 has been amended to more clearly indicate that the GABA<sub>A</sub> receptor 1 promoter P1a or GABA<sub>A</sub> receptor 1 promoter P1b or a functionally modified form thereof or an active fragment thereof, i.e., whichever nucleic acid segment functions as a promoter, is coupled to the reporter gene so that expression of the reporter gene is under the control of the promoter, modified form or active fragment.

New claims 32-41 have been added. Each of new independent claims 32 and 37 is based on originally-filed claim 23, support for the new claims being found therein. Specifically, new claim 32 recites that the promoter element of the expression system is selected from the group consisting of the nucleic acid molecules recited in claim 23 and also those nucleic acid molecules having at least 95% homology to either SEQ ID NO: 1 or SEQ ID NO: 2, support for the latter amendment being found on page 6, lines 6-14 of the originally-filed specification. New claim 37 is parallel to claim 32 but recites that the promoter element of the recited expression system is a functionally modified form of or active fragment of the same group of nucleic acid molecules recited in claim 32.

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Further, where "stringent hybridization conditions" have been referred to in claims 32 and 37, the specific stringent hybridization conditions appearing on page 6, line 16-20 of the originally-filed specification are now explicitly recited.

Each of the dependent claims of claim 32, i.e., 33-36, and the dependent claims of claim 37, i.e., 38-41, parallel and find their support in originally-filed claims 24-27, respectively.

No new matter has been added by any of the amendments to the claims.

IV. Objections for lack of drawings

It is alleged that the subject matter of the application admits of illustration by a drawing to facilitate understanding of the invention. Hence, Applicant has been required to submit a drawing in order pursuant to 37 C.F.R. §1.81. Applicants respectfully traverse the present objection and requirement for the following reasons.

Figures 4 and 5 of the originally-filed application clearly illustrate numerous examples of the promoter-reporter gene constructs which are at the heart of the presently-claimed screening methods. Figure 4 specifically shows both full-length and truncated active fragment forms of the GABA<sub>A</sub> receptor 1 promoter P1a and the GABA<sub>B</sub> receptor 1 promoter P1b operably

linked to the luciferase reporter gene. Data demonstrating the operable linkage, i.e., that luciferase expression is under the control of the coupled promoter or promoter fragment is also shown in Figure 4. (See also Example 5, Activity of GABA<sub>A</sub> R1 promoter P1a and P1b fragments at page 19, line 5 - page 20, line 4 of the originally-filed specification.)

Figure 5 and Table 2 specifically show functionally equivalent modified forms, in this case point mutants, of the promoters. (See also Example 6 Mutational analysis of P1a and P1b promoter element function, at page 20, line 6 - page 22, line 17 of the originally-filed specification.)

Further, the amendment of claim 22 herein to more particularly and clearly recite what Applicants regard as their invention has further obviated an additional drawing in order to facilitate the understanding of the invention.

In view of the above, withdrawal of the objection for lack of drawings and withdrawal of the requirement for further drawings are requested.

V. Claim rejections under enablement requirement of 35 U.S.C. §112, first paragraph

Claims 22-27 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. The present

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rejections essentially rely on two assertions: (1) that neither expression of GABA<sub>B</sub> receptors in host cells (claim 25) nor integration of GABA<sub>B</sub> promoters into the "genome" of the host cells is taught in an enabling fashion (claims 22-27), and (2) that the disclosure is not commensurate with the scope of the claims, since allegedly the disclosure does not teach a skilled artisan how to readily obtain the claimed functionally equivalent forms of the GABA<sub>B</sub> receptor 1 promoters P1a or P1b. (See Office Action, page 3, ¶3.) Applicants traverse the present claim rejections for the following reasons.

First, only claim 25 requires that the host cell express a GABA<sub>B</sub> receptor at all. Thus, this basis of rejection can only apply to claim 25. In any case, claims 22-27 are generally directed to the use of GABA<sub>B</sub> receptor 1 promoters P1a and P1b or functional equivalents which are operably linked to reporter genes. Examples 2-4 and Figures 2 and 3 of the originally-filed specification give a detailed, enabling description and actual examples of the construction of the promoter-reporter gene constructs and their use in screening.

Second, contrary to the Examiner's assertion, a teaching of how the GABA<sub>B</sub> receptor 1 promoters are integrated into the genome of the host cells is not required at all. Nothing in the disclosure limits the invention to genome-integrated copies of

the claimed constructs. Instead, transient transfection assays using, for example, non-genome-integrating plasmid-based expression vectors, as well-established in the art, can be used. Moreover, preparation of the type of transcriptional activation assay constructs recited in the presently rejected claims, whether disposed on an independent vector or within the host cell's genome, is a matter of routine experimentation and conventional. In connection with claim 25, cellular hosts endogenously expressing GABA<sub>A</sub> receptors themselves may clearly be derived from primary tissue cells which express these receptors or may be developed according to standard methods from other cells.

Third, the Examiner's assertions that the specification provides no guidance or working examples of promoter nucleic acids other than SEQ ID NOS: 1 and 2, nor teaches one skilled in the art how to use promoter sequences other than SEQ ID NOS: 1 or 2, nor teaches one how to obtain the claimed promoter sequences or functionally modified forms or active fragments (see Office Action, page 4, lines 3-18) are incorrect. The application is replete with disclosure enabling a skilled artisan to obtain the GABA<sub>A</sub> receptor 1 promoters and functionally modified equivalents and active fragments thereof, and how to use them, as shown in Examples 4-6, Table 2 and Figures 4 and 5 of the originally-filed specification. Further, these sections

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of the originally-filed specification provide not only an enabling disclosure of obtaining functional equivalents, such as active mutants and active fragments of the promoters, but also numerous actual examples thereof.

Moreover, in further response to the Examiner's assertion that the specification fails to disclose how functionally modified forms or active fragments of the GABA<sub>B</sub> receptor 1 P1a and P1b promoters can be identified and obtained, Applicants further note that the experiments of Examples 5 and 6 are directed, successfully, to this very purpose. The numerous actual examples of functionally-equivalent modified forms and active fragments shown in Figures 4 and 5 attest to the fact that the presently rejected claims are of a scope commensurate with the disclosure of the originally-filed application.

VI. Claim rejections under written description requirement 35 U.S.C. §112, first paragraph

Claims 22-27 are rejected under the written description requirement of 35 U.S.C. §112, first paragraph, since the specification allegedly does not reasonably convey that the inventors had possession of the genus asserted, by the Examiner, to be claimed by Applicants, i.e., GABA<sub>B</sub> receptor 1 P1a and P1b promoters and functionally-equivalent modified forms and active

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fragments thereof and those sequences hybridizing to the P1a or P1b promoters under stringent conditions. (See Office Action, page 3, ¶4.)

With respect to the promoters and functionally-equivalent modified forms and active fragments thereof, the present rejections for written description are analogous to the claim rejections for alleged lack of enablement. The following sections of the originally-filed specification concretely demonstrate Applicants were in actual possession the claimed functionally equivalent modified promoter forms and active promoter fragments.

Figures 4 and 5 of the originally-filed application clearly illustrate numerous examples of the promoter-reporter gene constructs which are at the heart of the presently-claimed screening methods. Figure 4 specifically shows both full-length and truncated active fragment forms of the GABA<sub>B</sub> receptor 1 promoter P1a and the GABA<sub>B</sub> receptor 1 promoter P1b operably linked to the luciferase gene. Data demonstrating the operable linkage, i.e., that luciferase expression is under the control of the coupled promoter or promoter fragment is also shown in Figure 4. (See also Example 5, Activity of GABA<sub>B</sub> R1 promoter P1a and P1b fragments at page 19, line 5 - page 20, line 4 of the originally filed specification.)

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Figure 5 and Table 2 specifically show functionally-equivalent modified forms, in this case point mutants, of the promoters. The activity of the promoter-reporter constructs is also shown in Figure 5. (See also Example 6 Mutational analysis of P1a and P1b promoter element function, at page 20, line 6 - page 22, line 17 of the originally-filed specification.)

In connection with "those sequences hybridizing to the P1a or P1b promoters under stringent conditions," the USPTO publication, Synopsis of Application of Written Description Guidelines ("the Synopsis"), particularly Example 9 Hybridization, suggests that (1) amendment of the claims to recite the exact hybridization conditions should not be required when such conditions are detailed in the specification and (2) hybridization under stringent conditions is conventional in the art. (A copy of Example 9 of the Synopsis is enclosed.) Example 9 of the Synopsis shows that this is especially the case when a claim limits the promoter sequence to one which is functional, as the presently-rejected claims do.

Notwithstanding the above traversals, Applicants have also added new claims 32-41 which specifically recite, directly or indirectly, either (1) the stringent conditions specifically disclosed in page 6, lines 16-20 of the originally-filed

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specification or, as shown to be permitted in Example 9 of the Synopsis, that (2) the nucleic acid sequence encoding the promoter has at least 95% nucleotide sequence homology to GABA<sub>A</sub> receptor 1 promoters P1a or P1b, as disclosed on page 6, lines 6-14 of the originally-filed specification.

In view of the above, withdrawal of the claim rejections under 35 U.S.C. §112, first paragraph is requested.

VII. Claim rejections under 35 U.S.C. §112, second paragraph

Claim 23 is rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness since, the recited "stringent conditions" for hybridization are allegedly not described. (See Office Action, page 5, ¶5.) Presumably this rejection was also meant to apply to claims 22 and 24-27.

However, stringent conditions for hybridization are described in detail on page 6, lines 16-20 of the originally-filed specification. Moreover, as described above with respect to the written description requirement of 35 U.S.C. §112, first paragraph, such stringent hybridization conditions are well known in the art. Hence, there is no indefiniteness with respect to the expression "stringent conditions" as recited in the presently-rejected claims. Withdrawal of the present claim

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rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

Further, notwithstanding the above traversal, Applicants note again that new claims 32-41 recite the details of the stringent hybridization conditions disclosed on page 6, lines 16-20 of the originally-filed specification or that the nucleic acid sequence encoding the promoter has at least 95% nucleotide sequence homology to GABA<sub>B</sub> receptor 1 promoters P1a or P1b, as disclosed on page 6, lines 6-14 of the originally-filed specification.

**MARKED-UP VERSION SHOWING REVISIONS TO CLAIMS**

22. (Twice Amended) A method for screening compounds for modulation of GABA<sub>B</sub> receptor 1 transcription, comprising the steps of:

(a) providing [transfected] a host cell hosting an [with a suitable] expression system comprising a nucleic acid molecule constituting a human GABA<sub>B</sub> receptor 1 promoter P1a and/or a human GABA<sub>B</sub> receptor 1 promoter P1b, or functionally equivalent modified forms thereof, or active fragments thereof, wherein the promoter or modified form thereof or active fragment thereof is coupled to a reporter gene so that expression of the reporter gene is under the control of the promoter, modified form or active fragment;

(b) contacting a test compound with the cell; and

(c) determining whether the test compound modulates the level of expression of the reporter gene.

26. (Twice Amended) The method according to claim 22, wherein the host cell hosts an [is further transfected with a suitable] expression system comprising a nucleic acid molecule encoding at least one transcription factor.

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CONCLUSION

Applicants have completely responded to the Office Action. For the foregoing reasons, withdrawal of the restriction requirement is deemed proper and hereby requested. Claims 1-41 are pending in the application and are in condition for examination and allowance, which action is earnestly solicited. The Assistant Commissioner is hereby authorized to charge any fee due in connection with this communication to Deposit Account No. 23-1703.

Dated: June 6, 2002

Respectfully submitted,



Paul Diamond  
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Agent for Applicants

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Enclosures

1. Abstract of Mu et al. The mouse GABA(A) receptor alpha3 subunit gene and promoter, Brain Res. Mol Brain Res. 67: 137-147, 1999
2. Example 9 Hybridization of USPTO publication Synopsis of Application of Written Description Guidelines

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1: Brain Res Mol Brain Res 1999 Apr 6;67 (1):137-47

Transcriptional regulation of GABAA receptor gamma2 subunit gene.

Mu W, Burt DR.

Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD 21201-1559, USA.

We have cloned the promoter regions of the genes for the mouse and human gamma<sub>2</sub> subunits of the type A receptors for gamma-aminobutyric acid (GABA). For the mouse, the two major transcription start sites were at +1 (by definition) and +43, as established by rapid amplification of cDNA ends (RACE) and primer extension. This numbering places the start methionine at +297. There was no TATA or CCAAT box. Both mouse and human sequences have a candidate neuron-restrictive silencer element (NRSE) site in the first intron (+956 in mouse). We made assorted mouse-based promoter/reporter (luciferase) constructs starting from a core extending from -331 to +136, varying sizes at both ends, and including and excluding the putative NRSE and more proximal sequences. These were tested by transient transfection in several neuron-like and non-neuronal cell lines. Both proximal and distal downstream elements appeared to help direct expression to neuron-like cells, the NRSE in the intron, by expression in non-neurons, and a 24-bp portion of the 5' untranslated region starting at +113 (named GPE1) by preferentially promoting expression in neuron-like cells. Cotransfected human NRSF (transcription factor for NRSE) reduced reporter expression in neuron-like cells for constructs containing the NRSE in two locations. In gel mobility shift assays, the mouse gamma<sub>2</sub> NRSE and a consensus NRSE both bound in vitro translated NRSF very similarly, and the NRSF gave the same major shifted band with the mouse gamma<sub>2</sub> NRSE as was observed with nuclear extracts. Copyright 1999 Elsevier Science B.V.

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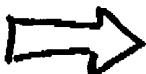
## Synopsis of Application of Written Description Guidelines

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e.g. expression vectors, the necessary common attribute is the ORF (SEQ ID NO: 2).

Weighing all factors including (1) that the full length ORF (SEQ ID NO: 2) is disclosed and (2) that any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicant was in possession of the genus of DNAs that comprise SEQ ID NO: 2.

**Conclusion:** The written description requirement is satisfied.



### Example 9: Hybridization

**Specification:** The specification discloses a single cDNA (SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification includes an example wherein the complement of SEQ ID NO: 1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity. The hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. These sequences may or may not be the same as SEQ ID NO: 1.

### Claim:

An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1,

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wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

**Analysis:**

A review of the full content of the specification indicates that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function. The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing.

The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity.

The search of the prior art indicates that SEQ ID NO: 1 is novel and unobvious.

There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.

There is actual reduction to practice of the disclosed species.

Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of

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skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

**Conclusion:** The claimed invention is adequately described.